Indian Journal of Chemistry
Vol. 54B, August 2015, pp 958-964

# Diastereoselective synthesis of tetrahydrofuran unit of (±)-6′-*epi*-varitriol from 5-oxabicyclo[2.1.1]hexane derivative

Surendra H Mahadevegowda[b] & Faiz Ahmed Khan*[a]

[a]Department of Chemistry, Indian Institute of Technology Hyderabad, Ordnance Factory Estate, Yeddumailaram 502 205, India

[b]Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208 016, India

E-mail: faiz@iith.ac.in

*Received 24 November 2014; accepted (revised) 10 June 2015*

A highly diastereoselective approach leading to tetrahydrofuran unit of an unnatural (±)-6′-*epi*-varitriol starting from an in-house 5-oxabicyclo[2.1.1]hexane derivative is reported. The resultant *anti*-alcohol *via* diastereoselective reduction of a γ,δ-unsaturated ketone has been subjected to 5-exo-trig iodoyclization using iodine and subsequent hydrogenolysis which affords titled tetrahydrofuran derivative. The prepared acyclic unsaturated polyol is a six-carbon sugar analogue and hence a carbocycle to carbohydrate route has been demonstrated.

**Keywords**: *epi*-Varitriol, 5-oxabicyclo[2.1.1]hexane, diastereoselective, reduction, iodocyclization

During past eight years a marine-derived natural product called (+)-varitriol **1** (**Figure 1**) became one of the most attractive target to various synthetic groups[1a]. The compound **1** was isolated by Barrero *et al*. in 2002 (Ref 1b) and later absolute configuration was established[1c]. The biological features evaluation for compound **1** showed potent cytotoxicity towards human cancer cell lines[1d,2a]. The synthesis of THF unit of the natural product was achieved using carbohydrate based chiral pool starting materials like methyl-α-D-mannopyranoside[2a], D-mannitol[2b], D-(–)-ribose[2c-g], and γ-D-ribonolactone[2h,i]. Additionally, strategies involving Au(III)-catalyzed cycloisomerization of α-hydroxy allene[3a], CSA induced epoxide ring opening[3b], and Pd(II)/Cu(II)-catalyzed bicyclization[3c] reactions have been developed for the synthesis of **1**. Njardarson *et al*. reported a total synthesis of (±)-varitriol *via* diastereoselective $Cu(hfacac)_2$ catalyzed vinyl oxirane ring expansion reaction[3d]. Moreover, a formal synthesis of **1** involving a key reaction Pd(II)/Cu(II) catalyzed bicyclization of unsaturated polyol starting from D-glucose is also reported[3e]. The high cytotoxicity of the natural product drew the attention of various synthetic chemists to prepare unnatural stereoisomers[2b] and structural analogues of **1** (Ref 2f, 3a,f). The total synthesis of (+)-6′-*epi*-varitriol **2** has been achieved by Srihari and coworker from D-(–)-ribose by employing Corey Chaykovsky reaction[2g]. We previously disclosed a formal synthesis[4] of varitriol **1** *via* lead (IV)-acetate mediated oxidative cleavage reaction by utilizing major epimer of THF tricarboxylate derivative which is obtained from Grob-type fragmentation of a 5-oxabicyclo[2.1.1]-hexane derivative[5]. Here, we wish to report a diastereo-selective route for the synthesis of THF unit of **2** from unseparated mixture of THF epimers *via* an acyclic 6-carbon sugar analogue[6] by using zinc mediated reductive cleavage reaction.

## Results and Discussion

In continuation of the present research interest on the exploration of constrained 5-oxabicyclo[2.1.1]-hexane derivatives[7] *via* an efficient Lewis acid mediated Grob-type fragmentation, the initial plan was to develop THF ring opening and cyclizing strategy to synthesize diastereomerically pure THF moiety of **1**. The retro-synthetic pathway for the current approach for the construction of THF unit of **1** from compound **3** *via* zinc mediated reductive cleavage of furanyl iodides **8a**,**b** is depicted in **Scheme I**.

Here, the mixture of THF tricarboxylates **4a**,**b** (dr = 88:12) were transformed into corresponding triols **5a**,**b** by reduction with $NaBH_4$ in 72% yield (**Scheme II**). The THF monoalcohols **6a**,**b** along with mixed acetals **7a**,**b** were obtained after subjecting triols **5a**,**b** for acetonide protection. Thereafter, the mixed acetals **7a**,**b** were converted into **6a**,**b** by treatment with PPTS in MeOH (Ref 4).

After the preparation of furanyl alcohols **6a**,**b**, to accomplish the synthesis of THF unit of (±)-varitriol *via* 5-exo-trig cyclization of unsaturated alcohol **13a**, the diastereomeric mixture of alcohols (**6a**,**b**) were converted to TBDPS ether protected γ,δ-unsaturated ketone **12** as depicted in **Scheme III**. The furanyl iodides **8a**,**b** were prepared in a fashion similar to a previous report (88% yield)[4], followed by zinc mediated reductive cleavage of iodides **8a**,**b** to afford an unsaturated tertiary alcohol **9**. The chemoselective deprotection of 6-membered acetonide of **9** with PPTS (10 mol%) in MeOH at 50°C gave triol **10** along with acetonide shuffled[8a] isopropylidene **11** (dr = 1:1) as by-product in 8% yield. The oxidative cleavage of triol **10** using $NaIO_4$ in THF:$H_2O$ (1:1) and the TBDPS ether protection for the resultant acyloin afforded a γ,δ-unsaturated ketone **12**.

Having ketone **12**, we turned our attention to prepare desired *anti*-alcohol **13a**. The details of diastereoselective reduction of ketone **12** with $NaBH_4$ (Ref 6b,8b), (*R*)-CBS[8c] and L-selectride[8d] are summarized in **Scheme IV**. The diastereoselectivity in reduction of ketone **12** is mainly affected by TBDPS group and β-substituents. For the less bulky reagent ($NaBH_4$) good *anti*-selectivity was observed (*anti*:*syn* = 21:3), moderate in case of (*R*)-CBS and little *anti* diastereoselectivity was observed in case of a bulky reagent like L-selectride employed for reduction. The reason is because of presence of bulky silyl group, in case of $NaBH_4$ *anti*-reduction is more preferable due to less steric hindrance between silyl group and incoming reagent. Whereas, in the case of (*R*)-CBS and L-selectride, due to greater steric hindrance of silyl

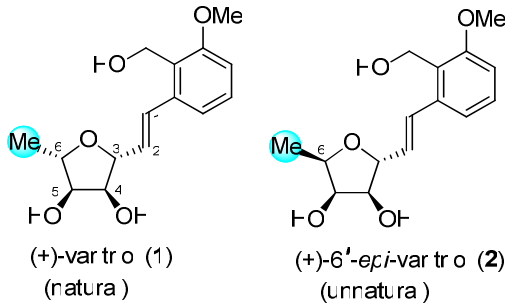
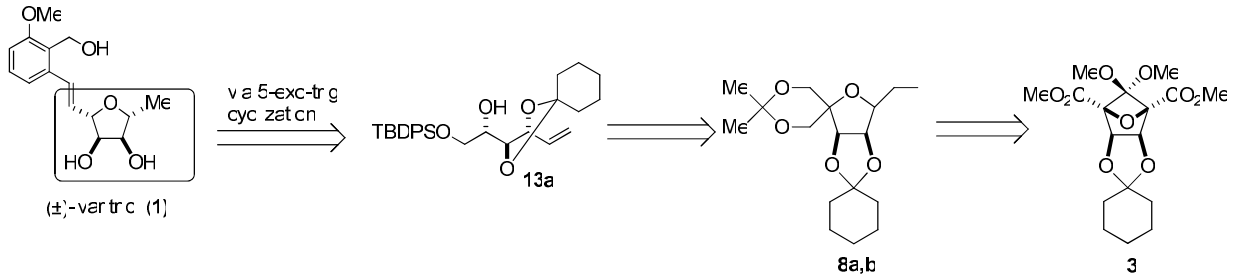
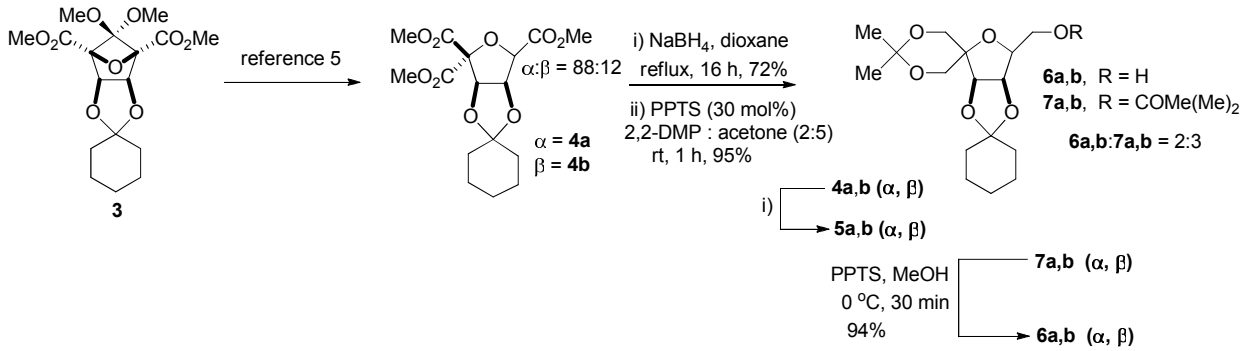


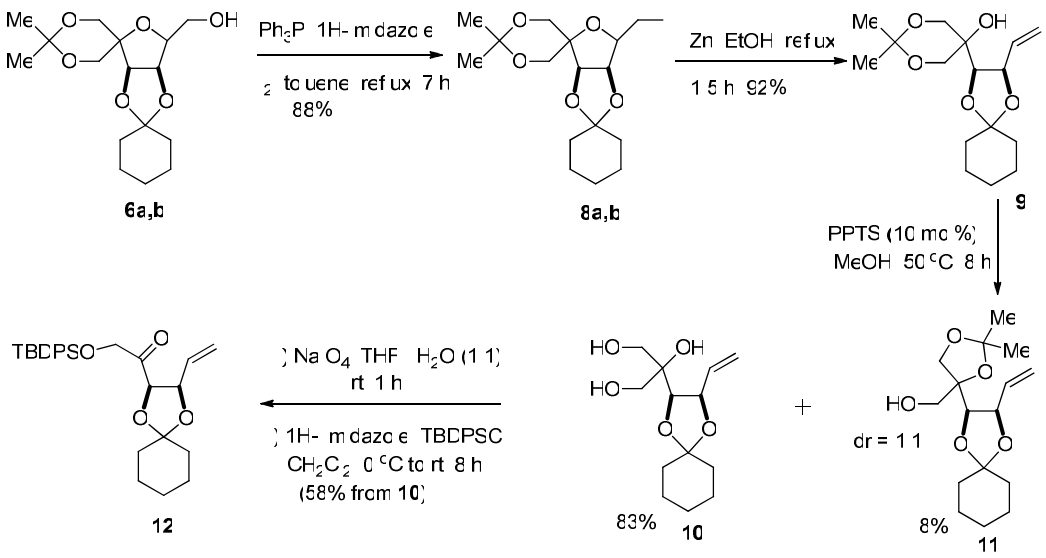

**Figure 1** — Structures of (+)-varitriol **1** and (+)-6′-*epi*-varitriol **2**



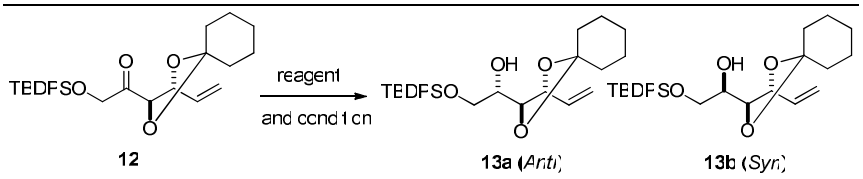

**Scheme I** — Proposed retrosynthetic route for THF unit of varitriol **1** from oxabicycle **3** *via* iodocyclization of **13a**




**Scheme II** — Synthesis of furanyl monoalcohols **6a**,**b** from oxabicycle **3**




**Scheme III** — Synthesis of γ,δ-unsaturated ketone **12** from alcohols **6a**,**b**




| Entry | Reagent and condition | Yield[a] (%) | **13a**:**13b** [*Anti*:*Syn*][b] |
|---|---|---|---|
| 1 | $NaBH_4$, EtOH, –78°C, 3 h | 99 | 21:3 |
| 2 | (*R*)-CBS, $BH_3.SMe_2$, THF, –78°C to –50°C, 4 h | 42 | 10:3 |
| 3 | L-selectride, THF, –78°C, 2 h | 98 | 5:4 |

[a]Isolated yield of products. [b]dr was determined from $^1$H NMR of crude reaction mixture.

**Scheme IV** — Reduction of ketone **12**

group and the reagent during *anti*-addition, the *syn* alcohol **13b** was obtained in considerable amount. The models for diastereoselectivity in *syn* and *anti*-reduction of **12** are represented in terms of Newman projection (**Figure 2**) (Ref 8d).

When diastereomerically pure alcohol **13a** was subjected to 5-exo-trig iodocyclization using $I_2$, $NaHCO_3$ in MeCN (1 h) at 0°C, a furanyl iodide **14** was obtained as a single diastereomer in 83% yield (**Scheme V**). At this stage, an attempt was made to control the stereochemistry during iodocyclization to get the required stereochemistry for THF of **1** by protecting alcohol **13a** as benzyl ether[9]. The treatment of alcohol **13a** with NaH/BnBr, TBAI in THF gave a complex mixture because of the presence of adjacent TBDPS ether group. Eventually, the iodide **14** was converted into the corresponding methyl substituted THF **15** in 94% yield by treatment with $Et_3N$ and 10% Pd/C under $H_2$ atmosphere[4] and the stereochemistry of THF **15** was confirmed by $^1$H-$^1$H COSY and $^1$H-$^1$H NOESY experiments. The tetrahydrofuran **15** is a potential precursor for the synthesis of (±)-6′-*epi*-varitriol **2**.

## Experimental Section

$^1$H and proton decoupled $^{13}$C NMR spectra were recorded at 400 and 100 MHz respectively, unless recorded at 500 ($^1$H NMR) and 125 MHz ($^{13}$C NMR). The samples for NMR were made by dissolving in $CDCl_3$. The δ value for the peaks in $^1$H NMR were reported in terms of ppm with reference to $CDCl_3$ (δ 7.26) peak and the coupling constants were reported in Hz. The multiplicity are reported as follows br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The chemical shift in $^{13}$C NMR is assigned by fixing middle peak of $CDCl_3$ at δ 77.00. The $^1$H-$^1$H COSY and $^1$H-$^1$H NOESY experiments were carried

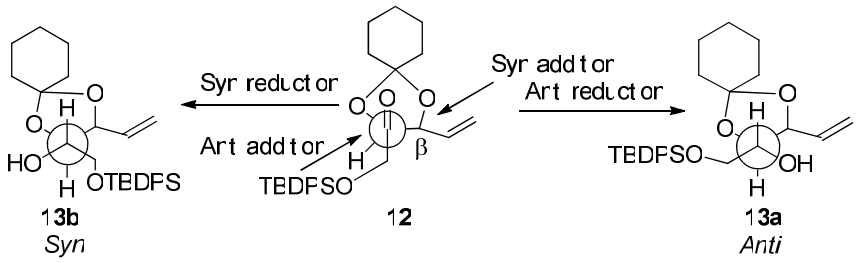
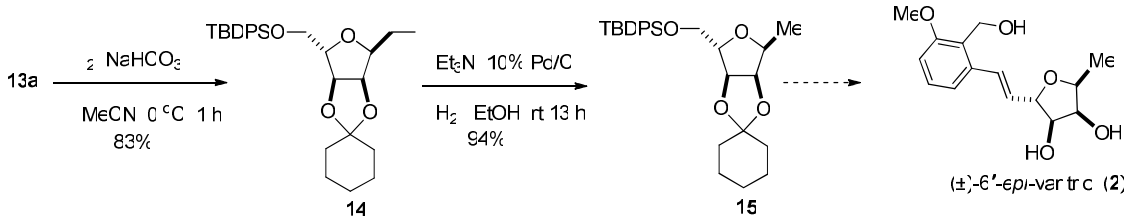



**Figure 2** — Models for diastereoselectivity in reduction of ketone **12**




**Scheme V** — The synthesis of THF unit of **2** *via* iodocyclization of alcohol **13a**

out to confirm the relative stereochemistry of the THF **15**. The IR spectra were recorded as neat (solids and liquids), unless in the form of KBr pellets for some solids. The HRMS analysis was carried out in ESI mode using Waters Q-TOF, unless in APCI mode using Agilent 6538 UHD Q-TOF mass spectrometer. Melting points were recorded in open capillary tubes and are uncorrected.

**Triol, 5b**: For the experimental procedure see reference 4, minor epimer, colorless liquid, $R_f$= 0.3 (100% EtOAc, silica gel TLC). IR (neat): 3380 (br), 2933, 2859, 1419, 1368, 1285, 1106, 1028 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 4.80 (dd, *J* = 5.9, 4.4 Hz, 1H), 4.56 (d, *J* = 5.4 Hz, 1H), 4.01-4.08 (m, 2H), 3.75-3.84 (m, 4H), 3.62 (br s, 2H), 2.87 (br s, 2H), 1.68 (d, *J* = 5.4, 2H), 1.60 (d, *J* = 3.4 Hz, 2H), 1.52 (br s, 4H), 1.37 (br s, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 113.6, 85.9, 82.6, 81.3, 80.0, 62.9, 61.8, 61.6, 35.4, 33.7, 24.9, 23.9, 23.5; HRMS (APCI): *m/z* Calcd for $C_{13}H_{26}NO_6$ $[M+NH_4]^+$ 292.1760. Found 292.1749.

**Monoalcohol, 6b**: For the experimental procedure see reference 4, minor epimer, colorless solid (m.p. 88-90°C), $R_f$= 0.35 (50% EtOAc in Hexane, silica gel TLC). IR (neat): 3455 (br), 2936, 2862, 1450, 1371, 1094, 1075 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 4.81-4.83 (m, 1H), 4.75 (dd, 1H, *J* = 5.9 Hz), 4.1 (dd, 1H, *J* = 12, 1.2 Hz) 3.87 (br s, 3H), 3.78 (dd, 2H, *J* = 11.7, 8.3 Hz), 3.58 (dd, 1H, *J* = 11.7, 1.5 Hz), 2.21 (br s, 1H), 1.64-1.74 (m, 3H), 1.49-1.63 (m, 5H), 1.46 (s, 3H), 1.42 (s, 3H), 1.30-1.48 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 113.8, 98.6, 82.3, 80.8, 79.0, 78.2, 63.6, 62.0, 61.5, 35.5, 34.1, 25.6, 25.0, 23.9, 23.6, 21.4; HRMS (ESI): *m/z* Calcd for $C_{16}H_{26}O_6$ $[M]^+$ 314.1729. Found 314.1737.

**Tertiary alcohol, 9**: To a stirred solution of iodides **8a**,**b** (1.2 g, 2.83 mmol) in dry EtOH (25 mL) was added zinc dust (1.85 g, 28.3 mmol) and refluxed. After 1.5 hr, the reaction mixture was brought to RT and solvent was evaporated. The residue was dissolved in EtOAc, filtered, washed with EtOAc, the combined filtrate washed with $H_2O$ (10 mL), organic layer was separated, the aqueous layer was extracted with EtOAc (2×15 mL), the combined organic layers were washed once with brine (10 mL), finally dried over anhyd. $Na_2SO_4$ and concentrated. The $SiO_2$ column chromatography (5-25% EtOAc in hexane) for the obtained residue afforded a reductively cleaved tertiary alcohol **9** (779 mg, 2.60 mmol), yield 92%, colorless viscous liquid, $R_f$= 0.4 (10% EtOAc in Hexane, silica gel TLC). IR (neat): 3425, 2991, 2938, 2864, 1718, 1450, 1373, 1201, 1077 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 6.15 (ddd, 1H, *J* = 17.3, 9.9, 7.6 Hz), 5.35 (dd, 1H, *J* = 17, 1.2 Hz), 5.24 (d, 1H, *J* = 10.5 Hz), 4.66 (t, 1H, *J* = 7.1 Hz), 4.27 (d, 1H, *J* = 6.7 Hz), 3.94 (t, 2H, *J* = 12.4 Hz), 3.64-3.72 (m, 2H), 2.77 (s, 1H), 1.36-1.72 (m, 10H), 1.42 (s, 3H), 1.39 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 135.1, 118.3, 108.9, 98.3, 78.4, 77.4, 68.5, 66.1, 65.5, 37.1, 34.3, 25.0, 24.5, 24.0, 23.7, 22.4; HRMS (ESI): *m/z* Calcd for $C_{16}H_{26}NaO_5$ $[M+Na]^+$ 321.1678. Found 321.1670.

**Triol, 10**: To a solution of compound **9** (778 mg, 2.60 mmol) in MeOH (25 mL) was added pyridinium *p*-toluenesulfonate (66 mg, 0.26 mmol), then the reaction mixture was warmed at 50°C, after 8 hr, the solvent

was removed under reduced pressure. The residue was purified by $SiO_2$ column chromatography (10-60% EtOAc in hexane) to afford a triol **10** (557 mg, 2.16 mmol), yield 83%, and monoalcohols **11** (62 mg, 0.21 mmol), yield 8%. Compound **10**: colorless liquid, $R_f$= 0.3 (50% EtOAc in Hexane, silica gel TLC). IR (neat): 3393, 2936, 2861, 1727, 1449, 1265, 1103, 1033 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 6.11-6.18 (m, 1H), 5.33 (d, 1H, *J* = 16.9 Hz), 5.24 (d, 1H, *J* = 10 Hz), 4.61 (t, 1H, *J* = 7.2 Hz), 4.22 (d, 1H, *J* = 6.3 Hz), 3.67-3.77 (m, 3H), 3.60 (dd, 1H, *J* = 11, 3.9 Hz), 3.14 (s, 1H), 2.87 (br s, 1H), 2.75 (br s, 1H), 1.63-1.74 (m, 3H), 1.50-1.62 (m, 5H), 1.39-1.43 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 135.4, 118.1, 108.8, 79.3, 78.7, 74.2, 65.2, 64.0, 37.3, 34.4, 24.9, 24.0, 23.7; HRMS (ESI): *m/z* Calcd for $C_{13}H_{22}NaO_5$ $[M+Na]^+$ 281.1365. Found 281.1360.

**Monoalcohols, 11**: Inseparable diastereomers (1:1), colorless liquid, $R_f$= 0.5 (25% EtOAc in hexane, silica gel TLC). IR (neat): 3460, 2936, 2861, 1640, 1450, 1370, 1213, 1058 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 6.03 (ddd, 1H, *J* = 17.3, 9.6, 8.9 Hz), 5.83 (ddd, 1H, *J* = 17.1, 10.2, 7.2 Hz), 5.34 (dd, 2H, *J* = 17.1, 10.4 Hz), 5.23 (t, 2H, *J* = 11.3 Hz), 4.59-4.62 (m, 2H), 4.49 (d, 1H, *J* = 6.4 Hz), 4.30 (d, 1H, *J* = 6.7 Hz), 4.13 (d, 1H, *J* = 8.6 Hz), 3.94 (dd, 2H, *J* = 23.8, 8.9 Hz), 3.79 (d, 1H, *J* = 8.6 Hz), 3.56-3.68 (m, 4H), 2.19 (br t, 2H, *J* = 6 Hz), 1.49-1.77 (m, 16H), 1.43 (s, 3H), 1.42 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.28-1.43 (m, 4H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 134.9, 134.7, 119.1, 118.1, 110.1, 109.7, 109.1, 108.9, 83.4, 83.1, 80.1, 78.7, 78.1, 77.9, 68.1, 67.9, 64.4, 64.0, 37.3, 36.9, 34.2, 34.1, 27.3, 27.0, 26.4, 26.0, 25.0, 24.9, 24.0, 23.9, 23.7, 23.6; HRMS (ESI): *m/z* Calcd for $C_{16}H_{26}NaO_5$ $[M+Na]^+$ 321.1678. Found 321.1673.

**Ketone, 12**: To a stirred solution of triol **10** (163 mg, 0.631 mmol) in THF:$H_2O$ (15:15 mL) was added $NaIO_4$ (149 mg, 0.694 mmol) at RT and reaction mixture was stirred vigorously for 1 hr. Then, reaction mixture was diluted with EtOAc and organic layer was separated, the aqueous part was extracted with EtOAc (2×15 mL), combined organic layers were washed once with brine, dried over anhyd. $Na_2SO_4$ and solvent was evaporated. The residue was purified by short $SiO_2$ column chromatography to afford an acyloin (87 mg, 0.385 mmol) as a colorless oil, the compound was dried under vacuum and dissolved in dry $CH_2Cl_2$ (10 mL). To a stirred solution of acyloin, 1H-imidazole (79 mg, 1.15 mmol), TBDPSCl (159 mg, 0.577 mmol) were added sequentially at 0°C, then the reaction mixture was warmed up to RT. After 8 hr, the reaction mixture was diluted with $H_2O$ (4 mL) and product was extracted with $CH_2Cl_2$ (3×15 mL), washed with brine (8 mL), dried over anhyd. $Na_2SO_4$ and concentrated. The $SiO_2$ column chromatography (2-8% EtOAc in hexane as eluent) for obtained crude oil afforded unsaturated ketone **12** (170 mg, 0.365 mmol), colorless viscous liquid, yield 58% (from 2 steps), $R_f$= 0.5 (4% EtOAc in Hexane, silica gel TLC). IR (neat): 2933, 2858, 1736, 1449, 1363, 1113 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.64-7.65 (m, 4H), 7.37-7.45 (m, 6H), 5.47-5.54 (m, 1H), 5.32 (d, 1H, *J* = 16.8 Hz), 5.11 (d, 1H, *J* = 10.4 Hz), 4.83-4.87 (m, 2H), 4.50 (d, 1H, *J* = 18.9 Hz), 4.24 (d, 1H, *J* = 18.9 Hz), 1.53-1.66 (m, 8H), 1.38 (br d, 2H, *J* = 4.9 Hz), 1.09 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 205.9, 135.6, 135.5, 132.6, 132.5, 129.9, 127.8, 127.7, 119.0, 111.1, 81.4, 77.9, 69.0, 36.4, 34.2, 26.7, 25.0, 23.9, 23.6, 19.2; HRMS (ESI): *m/z* Calcd for $C_{28}H_{40}NO_4Si$ $[M+NH_4]^+$ 482.2727. Found 482.2723.

***Anti*-alcohol, 13a**: A solution of $NaBH_4$ (14.8 mg, 0.391 mmol) in EtOH (5 mL) in a two necked round bottom flask was stirred at −78°C for 2 hr. Thereafter, a solution of ketone **12** (91 mg, 0.196 mmol) in EtOH (6 mL) was added dropwise *via* cannula, after additional stirring of reaction mixture for 3 hr, the solution was quenched with saturated aqueous $NH_4Cl$ (4 mL) and warmed up to RT. Then reaction mixture was diluted with $H_2O$ (4 mL), products were extracted with EtOAc (3×15 mL), the combined organic layers were washed once with brine (6 mL), dried over anhyd. $Na_2SO_4$ and concentrated. The $SiO_2$ column chromatography purification of crude afforded the alcohols **13a**,**b** (90.5 mg, 0.194 mmol), yield 99%, ratio of diastereomers (*anti*:*syn* = 21:03), the diastereomers were separated by preparative HPLC equipped with Jaigel-OA4100 column [0.1% *i*-PrOH in hexane (v/v) used as mobile phase]. Major diastereomer **13a**: $R_f$ = 0.4 (4% EtOAc in Hexane, silica gel TLC); colorless liquid. IR (neat): 3563, 2933, 2857, 1589, 1428, 1366, 1112 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.66-7.70 (m, 4H), 7.37-7.45 (m, 6H), 6.02 (ddd, 1H, *J* = 17.1, 10.4, 6.7 Hz), 5.42 (d, 1H, *J* = 17.1 Hz), 5.28 (d, 1H, *J* = 10.4 Hz), 4.7 (t, 1H, *J* = 6.4 Hz), 4.15 (dd, 1H, *J* = 9.2, 6.1 Hz), 3.85 (d, 2H, *J* = 4 Hz), 3.67-3.72 (m, 1H), 2.56 (d, 1H, *J* = 6.1 Hz), 1.48-1.61 (m, 8H), 1.37 (br d, 2H, *J* = 4 Hz), 1.07 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 135.6, 135.5, 134.1, 133.0, 132.9, 129.8, 129.7, 127.7 (2C), 117.7, 109.3, 78.4, 77.0, 69.8, 65.1, 37.6, 35.0, 26.8, 25.1, 23.9, 23.7, 19.3; HRMS (ESI): *m/z* Calcd for $C_{28}H_{39}O_4Si$ $[M+H]^+$ 467.2618. Found 467.2616.

***Syn*-alcohol, 13b**: Minor diastereomer **13b**: Colorless liquid, $R_f$ = 0.4 (4% EtOAc in Hexane, silica gel TLC).

IR (neat): 3509, 2931, 2856, 1427, 1365, 1109 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.65-7.72 (m, 4H), 7.36-7.44 (m, 6H), 5.94-6.01 (m, 1H), 5.2 (d, 1H, *J* = 17.2 Hz), 5.21 (d, 1H, *J* = 10 Hz), 4.55 (t, 1H, *J* = 7.6 Hz), 4.33 (dd, 1H, *J* = 6.9, 2.3 Hz), 3.63-3.69 (m, 3H), 2.41 (d, 1H, *J* = 5.2 Hz), 1.55-1.71 (m, 8H), 1.42 (br d, 2H, *J* = 5.4 Hz), 1.06 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 135.5, 134.5, 133.2, 133.1, 129.7 (2C), 127.7 (2C), 119.3, 109.2, 78.7, 76.6, 69.8, 64.8, 36.9, 34.4, 26.8, 25.1, 24.0, 23.6, 19.2; HRMS (APCI): *m/z* Calcd for $C_{28}H_{38}NaO_4Si$ $[M+Na]^+$ 489.2437. Found 489.2421.

**Furanyl iodide, 14**: To a stirred solution of **13a** (15 mg, 0.032 mmol) in a dry MeCN (1.5 mL) were added sequentially $I_2$ (16.3 mg, 0.064 mmol) in MeCN (1 mL) and $NaHCO_3$ (8.1 mg, 0.096 mmol) at 0°C. After 1 hr, was added saturated aqueous $NaHCO_3$ solution (1 mL), followed by addition of saturated $Na_2S_2O_3$ (2 mL), diluted with EtOAc and organic layer was separated. The aqueous part was extracted with EtOAc (2×12 mL), combined organic layers were washed with brine (4 mL), dried over anhyd. $Na_2SO_4$ and concentrated. The $SiO_2$ column chromatography for the crude liquid afforded iodide **14** (15.8 mg, 0.026 mmol), yield 83%, viscous liquid, $R_f$ = 0.5 (5% EtOAc in Hexane, silica gel TLC). IR (neat): 2932, 2857, 1390, 1333, 1110 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.66 (td, 4H, *J* = 7.3, 1.5 Hz), 7.39-7.44 (m, 6H), 4.92 (d, 1H, *J* = 5.9 Hz), 4.81 (dd, 1H, *J* = 5.9, 3.9 Hz), 4.51 (td, 1H, *J* = 6.8, 3.9 Hz), 4.16 (t, 1H, *J* = 2.9 Hz), 3.81 (dd, 1H, *J* = 11.2, 3.4 Hz), 3.68 (dd, 1H, *J* = 11.2, 3.4 Hz), 3.35 (dd, 1H, *J* = 9.5, 7.1 Hz), 3.24 (dd, 1H, *J* = 9.3, 6.8 Hz), 1.69-1.72 (m, 2H), 1.53-1.65 (m, 6H), 1.40 (br d, 2H, *J* = 4.9 Hz), 1.05 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 135.6, 135.5, 132.7, 132.6, 129.9, 129.8, 127.8 (2C), 113.2, 85.0, 83.3, 83.1, 81.1, 65.8, 36.0, 34.7, 26.8, 25.1, 24.0, 23.8, 19.0, 1.3; HRMS (ESI): *m/z* Calcd for $C_{28}H_{38}IO_4Si$ $[M+H]^+$ 593.1584. Found 593.1589.

**THF, 15**: To a stirred solution of iodide **14** (14 mg, 0.023 mmol) in EtOH (2 mL) were added triethyl amine (8 mg, 0.070 mmol) and 10% Pd-C (12 mg), and reaction mixture was stirred under an atmosphere of hydrogen (a bladder). After 13 hr, the solvent was removed under reduced pressure and the obtained crude compound was purified by $SiO_2$ column chromatography (6-10% EtOAc in hexane as eluent) to afford methyl substituted tetrahydrofuran **15** (10.0 mg, 0.021), yield 94%, viscous liquid, $R_f$ = 0.45 (5% EtOAc in Hexane, silica gel tlc). IR (neat): 2932, 2857, 1857, 1427, 1366, 1106 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.64-7.66 (m, 4H), 7.36-7.45 (m, 6H), 4.85 (d, 1H, *J* = 5.9 Hz), 4.61 (dd, 1H, *J* = 6.1, 4.2 Hz), 4.20-4.26 (m, 1H), 4.09 (t, 1H, *J* = 3.9 Hz), 3.76 (dd, 1H, *J* = 11.2, 4.1 Hz), 3.69 (dd, 1H, *J* = 11.2, 3.9 Hz), 1.72-1.75 (m, 2H), 1.56-1.65 (m, 6H), 1.4 (br d, 2H, *J* = 5.4 Hz), 1.29 (d, 3H, *J* = 5.9 Hz), 1.05 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 135.6, 135.5, 133.0, 132.9, 129.8, 129.7, 127.8 (2C), 112.7, 84.3, 83.1, 82.4, 78.1, 65.3, 36.0, 35.0, 26.8, 25.1, 24.0, 23.9, 19.1, 14.7; HRMS (ESI): *m/z* Calcd for $C_{28}H_{39}O_4Si$ $[M+H]^+$ 467.2618. Found 467.2612.

## Conclusion

A new synthetic route from oxa-bridged derivative leading to THF unit of (±)-6′-*epi*-varitriol has been described which is an unnatural isomer of novel anti-tumor natural product (+)-varitriol. The diastereomeric mixture of oxygenated THF derivatives were converted into titled THF derivative by employing zinc mediated reductive cleavage and diastereoselective iodocyclization reactions as key steps. The easily prepared acyclic unsaturated polyol is a six-carbon sugar analogue and hence an uncommon carbocycle to carbohydrate route has been demonstrated.

## Acknowledgement

FAK gratefully acknowledges CSIR, New Delhi for financial support. SHM thanks CSIR, New Delhi for research fellowship.

## References

1 (a) Majik M S, Tilvi S & Parvatkar P T, *Curr Org Synth*, 11, **2014**, 268; (b) Malmstrøm J, Christophersen C, Barrero A F, Oltra J E, Justicia J & Rosales A, *J Nat Prod*, 65, **2002**, 364; (c) Clemens R T & Jennings M P, *Chem Commun*, **2006**, 2720; (d) Mayer A M S & Gustafson K R, *Eur J Cancer*, 40, **2004**, 2676.

2 (a) Kumar V & Shaw A K, *J Org Chem*, 73, **2008**, 7526; (b) Ghosh S & Pradhan T K, *J Org Chem*, 75, **2010**, 2107; (c) Srinivas B, Sridhar R & Rama Rao K, *Tetrahedron*, 66, **2010**, 8527; (d) Zeng J, Seenuvasan V, Xiang S & Liu X-W, *Org Lett*, 13, **2011**, 42; (e) Nagarapu L, Paparaju V, Satyender A & Rajashaker B, *Tetrahedron Lett*, 52, **2011**, 7075; (f) Ghosal P, Sharma D, Kumar B, Meena S, Sinha S & Shaw A K, *Org Biomol Chem*, 9, **2011**, 7372; (g) Vamshikrishna K & Srihari P, *Tetrahedron*, 68, **2012**, 1540; (h) Karlubikova O, Palik M, Lasikova A, Kozisek J & Gracza T, *Synthesis*, 20, **2010**, 3449; (i) Caletková O, Lásiková A, Hajdúch M, Džubák P & Gracza T, *Arkivoc*, 6, **2012**, 365.

3 (a) Sun T, Deutsch C & Krause N, *Org Biomol Chem*, 10, **2012**, 5965; (b) Sudhakar G & Raghavaiah J, *J Org Chem*, 78, **2013**, 8840; (c) Palik M, Karlubikova O, Lasikova A, Kozisek J & Gracza T, *Eur J Org Chem*, 5, **2009**, 709; (d) Brichacek M, Batory L A, McGrath N A & Njardarson J T, *Tetrahedron*, 66, **2010**, 4832; (e) Palík M, Karlubíková O, Lackovicová D, Lásiková A & Gracza T, *Tetrahedron*, 66,

**2010**, 5244; (f) Senthilmurugan A & Aidhen I S, *Eur J Org Chem,* 3, **2010**, 555.

4 Mahadevegowda S H & Khan F A, *Tetrahedron Lett*, 55, **2014**, 2266.

5 Mahadevegowda S H & Khan F A, *Tetrahedron*, 69, **2013**, 8494.

6 (a) Perali R S, Mandava S & Bandi R, *Tetrahedron*, 67, **2011**, 4031; (b) Perali R S, Mandava S & Chunduri V R, *Tetrahedron Lett*, 52, **2011**, 3045.

7 (a) Khan F A, Dash J, Sudheer Ch, Sahu N & Parasuraman K, *J Org Chem*, 70, **2005**, 7565; (b) Mahadevegowda S H & Khan F A, *Tetrahedron Lett*, 55, **2014**, 4400.

8 (a) Khan F A & Rout B, *J Org Chem*, 72, **2007**, 7011; (b) Hoffman R V, Maslouh N & Cervantes-Lee F, *J Org Chem*, 67, **2002**, 1045; (c) Gille A & Hiersemann M, *Org Lett*, 12, **2010**, 5258; (d) Robertson J, Unsworth W P & Lamont S G, *Tetrahedron*, 66, **2010**, 2363.

9 White J D, Wang G & Quaranta L, *Org Lett*, 5, **2003**, 4109.